REMARKS

Claims 1-37, 77, 83-94, 97-108, 119, 121, and 123 are now pending in the application while claims 1-37, 77, 84-87, 93, 94, 97 and 101-108 are withdrawn from consideration. Claims 83, 88-92, 98-100, 119, 121, and 123 stand rejected. No claims are amended. Claims 1-37, 77, 83-94, 97-108, 119, 121, and 123 remain pending.

Consideration after a final rejection

Consideration after a final rejection is proper because the remarks place the claims in an allowable condition and require no further search or examination. Further and favorable consideration is solicited.

Rejoinder of withdrawn species claims

Upon finding that a generic claim 83 is patentable, Applicants respectfully request rejoinder of claims 84-87, 93, 94, 101-108 and 127-130. These claims were withdrawn from consideration by the Examiner pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species in the action mailed November 7, 2006. Since there is now an allowable generic claim 83, Applicants respectfully request rejoinder of the withdrawn claims. Applicants note that the withdrawn claims are listed as "previously presented" in the earlier prosecution. Nevertheless, Applicants respectfully request rejoinder.

Before addressing the outstanding rejection for anticipation and obviousness, Applicants offer the following remarks on the claimed subject matter and the advantages provided by the claimed subject matter. Following that, the response to the obviousness rejection is set forth in a way intended to clarify Applicant's position that a person of skill in the art would not combine the references. Further and favorable consideration is solicited in light of the following discussion.

The claimed subject matter

Claim 83 (the main independent claim) relates to a nucleic acid molecule which encodes a monomer, *i.e.* a single polypeptide. The *structure* of the encoded polypeptide can schematically be presented as:

AU – DM – TU

where AU is an antigenic unit, DM is a dimerization motif and TU is a targeting unit for an antigen presenting cell.

DM is further defined: it comprises an Ig hinge region and a Cγ3 domain (that is, DM is derived from an antibody).

Also, the entire polypeptide lacks a CH2 domain.

Finally, the polypeptide encoded by the claimed nucleic acid forms a dimeric molecule, which has the structure:

AU – DM – TU

|||

AU – DM – TU

where the symbol "|||" indicates the binding between the 2 units; said binding is according to the claim language constituted by 1) disulfide bridging between the Ig hinge regions of the two polypeptides and 2) hydrophobic interactions between the 2 Cγ3 domains of the two polypeptides.

So, the subject matter the skilled person has to arrive at from the prior art is an isolated nucleic acid, which encodes the polypeptide AU – DM – TU as defined above. This is a very important point when comparing the presently claimed invention with the disclosure in Herman, discussed below.

Advantages provided by the claimed subject matter

As has been shown by the documentation presented during Examination (notably by the Fredriksen reference), the claimed nucleic acid is useful for eliciting immune responses against molecules comprising epitopes corresponding to the antigenic unit in the expression product of the claimed nucleic acid. These immune responses have been demonstrated to be prolonged and also more vigorous than immune responses raised against the dimeric proteins (is demonstrated by the references submitted during Examination, in particular Fredriksen et al. 2006). To the best of Applicants' knowledge, superior immunogenicity exhibited by a DNA vaccine vs. the immunogenicity exhibited by the corresponding protein vaccine has not been reported before.

So, the patent motivating feature of the claimed nucleic acid is that it may be used in DNA vaccination for raising a prolonged and strong immune response against the antigenic unit encoded by the nucleic acid.

Obviousness

The Examiner alleges a *prima facie* case of obviousness by combining the teachings of Herman with the teachings of Slavin-Chiorini. Applicants respectfully traverse the rejection.

It is axiomatic that there can be no rejection for obviousness if the references when combined do not contain all of the features of the rejected claims.

In the present case, the primary reference by Herman would, if the obviousness rejection is correct, need to include ALL technical features of the claimed invention except for the modification(s) obtained from another prior reference. So, initially it is of value to investigate whether Herman unambiguously discloses a polypeptide, which has the structure AU - DM' - TU (where DM' is identical to DM discussed above, but also including a CH2 domain). (Slavin-Chiorini lacks such a disclosure).

Herman fails as a primary reference: it may be that all the generic elements are mentioned, but their structural organisation into one single polypeptide is absent

In order for an obviousness rejection over Herman in view of Slavin-Chiorini to be correct, Herman would have to disclose at least one embodiment of the "multi-specific ligands" taught therein, where one single polypeptide exhibits the structural organisation: antigenic unit – dimerization motif – targeting unit, where said dimerization motif besides lacking a CH2 domain includes an Ig hinge region and a Cγ3 domain and where the targeting unit is for an antigen presenting cell. This disclosure is missing from Herman.

1) Taking the latter issue first – the terms "antigen presenting cell" and its abbreviation "APC" occur in the following locations in Herman:

> §0072: This paragraph lists in tabular form a number of putative targets for the multifunctional ligands, and some of these are targets for antigen-presenting cells (e.g. dendritic cell markers). However, nowhere in the paragraph/table is it suggested that the 2 different ligands are part of the same polypeptide and are separated by an Ig hinge region and a Cγ3 domain.

§0137: Here it is suggested that the "first moiety" may comprise two different target ligands – it is in particular suggested that one ligand can bind an MHC peptide complex and the other can bind a ligand on an APC. Nowhere in the paragraph is it suggested that the 2 different ligands are part of the same polypeptide and are separated by an Ig hinge region and a Cγ3 domain.

§0143: In this paragraph, it is mentioned in a parenthesis that one of the at least 2 ligand binding moieties may bind to an antigen presenting cell. However, the location of this moiety relative to the other ligand binding moiety is not provided (in the paragraph, it is indicated that both moieties preferably antibodies) meaning that the paragraph i.a. describes a construct having a structure where the two moieties are located in separate polypeptides. No description is provided of a construct where one moiety is present in the same polypeptide and separated by a Cγ3 domain and an Ig hinge region.

§0148: This paragraph in essence teaches the same as §0143: Again, there is no mentioning that the 2 different ligand binding moieties are part of the same polypeptide.

§0171: In this paragraph, it is indicated that a "first portion" of the multi-specific ligand is "...fused, conjugated or otherwise linked directly or indirectly to an immunizing moiety..." which may be an antibody component that binds to an APC. Again, nothing in this paragraph indicated that the "first portion" and the "immunizing moiety" are separated by an Ig hinge region and a Cγ3 domain in the same polypeptide.

§0343: This paragraph (which both uses the term "antigen presenting cell and "APC") mentions that one of the ligand binding moieties may bind to a specific MHC peptide complex and thereby targets the heterofunctional ligand to an APC. Again, there is no teaching that the APC and the targeting moiety and the other moiety are part of the same polypeptide and are separated by a dimerization motif as defined in the present claims.

It is not sufficient for a finding of obviousness that Herman teach the presence of certain generic elements (CH3 domains, Ig hinge regions, CH2 domains, targeting units for antigen presenting cells) in the multispecific ligands. To properly support a rejection for obviousness it would be necessary for Herman to teach the same overall structural organisation of a polypeptide as presently claimed. So, absent any direct and unambiguous disclosure in Herman of a polypeptide having the structure AU - DM' - TU, the presently claimed invention must be unobvious over Herman in view of Slavin-Chiorini.

On the background of the express doubts stated in Slavin-Chiorini, the final rejection is based on the expectation of a much too high degree of cross-technology reproducibility of the technology taught by Slavin-Chiorini.

In addition to this, the following points should also be noted:

2) Slavin-Chiorini teaches that removal of a CH2 domain from a monoclonal murine antibody has the consequence that the specific antibody has a faster clearance rate (=lower serum half-life) than the corresponding unmodified monoclonal antibody. Nothing in Slavin-Chiorini gives the impression that this effect would also appear if modifying a "multi-specific ligand" like the ones taught in Herman.

To put this in perspective, even if Herman had disclosed a polypeptide having the structure AU - DM' - TU, which could form the dimeric structure:

AU-DM'-TU

|||

AU-DM'-TU

- there is nothing in Slavin-Chiorini that teaches or suggests that removal of a CH2 domain in the two monomers would have any beneficial effects on such an artificial molecule.

Here it is also important to note that Slavin-Chiorini's molecule is a murine antibody analogue used in diagnosis – the reference explicitly teaches that it may be valuable (but that it is not certain) that removal of the CH2 domain in such an antibody will generally decrease serum half-life – it is namely also underscored in Slavin-Chiorini that further testing is necessary and that other doubts as to the usefulness of the CH2 free antibodies are expressed:

> Page 102, right-hand column, lines 9-12 (studies of metabolic uptake planned when using other radionuclides); lines 24-28 (the CH2-domain free constructs differ in their chain assembly and comparative studies are necessary); and lines 31-33 (further clinical testing required because the CH2-free antibody exhibits reduced tumour binding).

For a skilled person to be motivated to modify Herman by using the approach taken in Slavin-Chiorini, he would have to have at least some hint or suggestion from either Herman or Slavin-Chiorini that Herman's constructs (which are not murine monoclonal antibodies) could somehow benefit from removal of the CH2 domain. But this suggestion is missing from the art.

Too little weight has been given to the fact that a person of skill would not combine the references as suggested.

3) Finally, the Examiner has underweighted Applicants' position (which is supported by the declaration by Sally Ward, *i.e.* a person skilled in the art) that the skilled person would not combine the Herman and Slavin-Chiorini references. The main argument, which has not been refuted by the Examiner, is based on 2 facts:

First of all, Herman only discusses the possibility of increasing serum half life (=decreasing clearance) of the multi-specific ligands. There is no mentioning in Herman that it would be of interest, let alone desirable, to decrease half-life (=increase clearance). One can conclude that Herman only aims at maintaining or increasing serum half life. This fits perfectly with the fact that Herman relates to the provision of therapeutic molecules, see paragraphs **0002** - **0005** in Herman.

Second, Slavin-Chiorini explicitly shows that removal of the CH2 domain in a murine monoclonal antibody decreases the serum half-life (=increases clearance) of the antibody. Slavin-Chorini thus indicates that this is a desirable feature for diagnostic applications where antibodies labelled with radionuclides are used.

Against this, the Examiner appears to argue that "...if clearance rate is an inventive feature of the claimed antibody structure, none of the instant claims even contain such language..."

But this is beside the point: Applicants' argumentation does not relate to the clearance rate of the claimed constructs, but rather to the apparent incompatibility of the Herman and Slavin-Chiorini references for the purposes of establishing a *prima facie* case of obviousness. Herman expresses that increased half-life of a multi-specific receptor is desirable and Slavin-Choirini reports decreased half-life when removing the CH2 domain of a murine antibody. The Examiner has not established how and why it would appear obvious to the skilled person, under these circumstances, to combine Herman with Slavin-Chiorini, even in a situation where Herman would actually disclose a molecule having the above-referenced structure AU – DM – TU (which it does not disclose).

In this connection, Applicants do not quite understand the last paragraph in the Office Action:

> "The examiner has yet to identify where in Herman increasing serum half-life is a requirement or inducement to delete CH2, further wherein according to the hereinabove excerpt, it's an option and is seemingly only achieved by mutating CH3"...

Applicants do not argue that Herman induces anyone to delete the CH2 to increase half-life; they simply urge that Herman teaches preserving or increasing serum half-life of multi-specific receptors, and further that neither of these two options combine naturally with the decreased half-life reported in Slavin-Chiorini.

CONCLUSION

For the reasons discussed above, Applicants believe that claims 1-37, 77, 83-94, 97-108, 119, 121, and 123 are in an allowable condition and respectfully request an early Notice of Allowance. In the alternative, Applicants request an Advisory Action stating whether the arguments can be considered at this time after final. The Examiner is invited to telephone the undersigned if that would be helpful to resolving any issues.

Respectfully submitted,

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By: /Robert M. Siminski/
Mark A.Frentrup, Reg. No. 41,026
Robert M. Siminski, Reg. No. 36,007

HARNESS, DICKEY & PIERCE, P.L.C.
P.O. Box 828
Bloomfield Hills, Michigan 48303
(248) 641-1600

RMS/MAF/cg/jo

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